

Combination of Electroconvulsive Therapy and Clozapine in the Treatment of Malignant Catatonia: a Case Report

結合電驚厥療法及氯氮平治療惡性僵木症：病例報告

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Abstract

A woman with treatment-resistant mania and malignant catatonia failed to respond to several of the conventional treatments including electroconvulsive therapy but showed a marked response to a combination of clozapine (250 mg daily) and electroconvulsive therapy within a few days of initiating treatment.

Key words: Antidepressive agents, tricyclic; Catatonia; Combined modality therapy; Electroconvulsive therapy; Schizophrenia

摘要

一名女性患有躁狂症及惡性僵木症，她對幾種傳統療法（包括電休克療法）未見起色。但病人接受結合電驚厥療法及每天服用250毫克的氯氮平數日後，病情有明顯改善。

關鍵詞：三環抗抑鬱藥、僵木症、綜合治療、電休克療法、精神分裂症

Introduction

Catatonia is a syndrome characterised by motor signs such as posturing, catalepsy, waxy flexibility, and rigidity. Behaviour may change suddenly, ranging between extremes of excitement and stupor, and may include staring, negativism, impulsivity, mannerisms, stereotypy, echolalia, echopraxia, and automatisms.^{1,2}

The severity of catatonia ranges from mild to lethal. Stauder first applied the term 'lethal catatonia' in 1934 to describe a life-threatening syndrome characterised by mounting fever, intense excitement, diverse catatonic presentations, followed by stupor and death. At the 1992 American Psychiatric Association meeting, a new term, 'malignant catatonia', was suggested as a replacement for lethal catatonia, based on the perception of decreasing mortality in this condition.³ Several authors have suggested use of the term 'simple or non-malignant catatonia' in the absence of autonomic instability or hyperthermia and 'malignant catatonia' when these symptoms are present.^{1,2}

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Neuroleptic malignant syndrome was first reported in the 1960s as a rare but potentially lethal complication of antipsychotic medication use.⁴ Neuroleptic malignant syndrome is clinically indistinguishable from malignant catatonia in many cases and it is speculated by many authors that it is an iatrogenic form of malignant catatonia.⁵ As a result, the term 'neuroleptic-induced catatonia' is also used to describe the condition.¹⁻³ Many investigators believe that catatonia is best understood as a final pathway for many central nervous system disorders and the only important difference is whether the syndrome arose spontaneously or whether it was triggered or accelerated by neuroleptic exposure.^{4,6} Various pharmacological and non-pharmacological methods of treatment have been described in the literature. Ungvari et al⁷ reviewed the pharmacological treatment of catatonia and concluded that benzodiazepines are an effective treatment for most of the symptoms and signs of catatonia. Patients who do not respond to benzodiazepines are treated with electroconvulsive therapy (ECT).² In malignant catatonia, emergency ECT is the treatment of choice. General supportive measures such as maintaining fluid balance and nutrition are important. Although antipsychotics are generally not recommended during a catatonic phase, as the risk of precipitating neuroleptic malignant syndrome is considerably increased, they may have a role in treatment-resistant cases.² Case reports have described the effectiveness of clozapine, risperidone, and a combination of olanzapine and ECT.⁸⁻¹⁰

We report a case of a woman in her fifties with treatment-resistant mania and malignant catatonia who failed to respond to several of the well-known treatments

but showed a marked response and made a full recovery after treatment with a combination of ECT and clozapine.

Case Report

Mrs B was a 50-year-old caucasian, married and employed lady. Her son was diagnosed as having bipolar affective disorder and a learning disability. She had worked as a nurse for more than 10 years, and as a nursing manager for about 6 months, prior to the episode we describe. She had a history of alcohol misuse extending back for the last 30 years.

She was admitted in July 2006 to an acute adult psychiatric unit after a mental health assessment initiated by the police. Two months prior to the psychiatric unit admission, she had been on holiday and had no symptoms suggestive of affective disorder at that time. She reported that she was unhappy after returning from holiday and started to drink excessive amounts of alcohol. She was assessed in the outpatient clinic and diagnosed as having a moderate depressive episode and was prescribed citalopram 20 mg daily, which she took for the week prior to admission to the psychiatric unit. During the assessment that led to hospital admission, she reported receiving messages from god and having the ability to read others' minds. She reported to have been "tested by the world's different religions". There was a history of elated mood, poor sleep, talkativeness, and preoccupation with religion. She told family members that she had won the lottery and gave away her belongings to others. She had grandiose delusions in the context of overactivity. She was diagnosed as experiencing a manic episode and admitted to the psychiatric unit.

Mrs B was agitated and overactive in hospital. She slept poorly, was sexually disinhibited and expressed grandiose ideas about controlling and predicting world events such as plane crashes and disasters. She was formally detained in hospital using the Mental Health Act and was transferred to the Psychiatric Intensive Care Unit (PICU) as she became difficult to manage.

She was initially prescribed olanzapine 10 mg daily and sodium valproate 400 mg daily. The dose was increased to olanzapine 20 mg daily and sodium valproate 600 mg twice daily by the fifth day of hospital admission. Lorazepam and haloperidol were prescribed on an as-needed basis. By day 28 of her admission, Mrs B had not responded to this initial regimen and a decision was taken by the PICU team to change the sodium valproate to lithium carbonate. She was started on an initial dose of 400 mg daily. Unfortunately, after 11 days this had to be discontinued due to the difficulty obtaining blood samples to monitor her lithium levels. There was no indication of any response to this dosage. She was given a trial of carbamazepine 200 mg twice daily for 7 days to which she also failed to show a response.

She deteriorated further from the 40th day of admission. She became confused, disoriented, and catatonic. She was overactive, agitated, rigid, tremulous, mute, feverish, confused with fluctuating levels of psychomotor activity. Her pulse fluctuated between 59 and 87 beats per minute

and her sitting blood pressure fluctuated between 119/72 and 157/87 mm Hg. Her food and fluid intake became poor. Urine dipstick tests showed the presence of blood, ketones, and protein. She was administered intravenous fluid due to her poor fluid intake. She had several investigations during her admission. Her electrocardiogram, urea and electrolytes, thyroid function tests, liver function tests (including gamma GT), C-reactive protein, B12 and folate levels were normal. A full blood count showed leukocytosis ($14.1 \times 10^9/L$) with increased neutrophils ($8.1 \times 10^9/L$). Investigations for systemic lupus erythematosus, metachromatic leukodystrophy, syphilis, meningitis, a urinary tract infection and septicaemia were negative. When her condition deteriorated, blood investigations showed a raised creatinine kinase level of 2605 IU/L. Her full blood count continued to show a leukocytosis ($13.7 \times 10^9/L$) with increased neutrophils ($10.7 \times 10^9/L$), although no source of infection could be found. An electroencephalographic recording and computed tomographic scan of the brain did not reveal any abnormalities. It was not possible to do a magnetic resonance imaging scan because of her agitation.

Following the investigations and a review by the medical and neurological teams, a diagnosis of resistant mania with malignant catatonia was made. She was prescribed high doses of diazepam 240 mg/day and lorazepam 12 mg/day. Olanzapine and haloperidol were stopped. It was decided to commence ECT because of her poor response to benzodiazepines and she had her first session of ECT on the 42nd day of admission. Electroconvulsive therapy was administered bilaterally using a Thymatron System-IV machine (frequency: 10-70 Hz, stimulus generation: bipolar brief pulse square wave, standard maximum output across 220 ohms impedance: 504 mC). The dose setting was between 40 and 200% and the impedance varied between 2000 and 3000 ohms. An electroencephalogram was recorded during all sessions. She received 12 bilateral ECTs and had a maximum of 200% administered on one occasion. Seizures varied between 14 and 34 seconds and the total seizure time was 233 seconds. Flumazenil 500 µg was administered before treatment to reverse the effects of the benzodiazepines. Her response to ECT was minimal and was sustained for only a few hours after each session.

At this stage she was transferred to a different psychiatric team. As she showed a poor response to conventional treatments for catatonia, a literature review was conducted to identify other interventions and it was decided to treat her with a combination of ECT and clozapine. Clozapine was introduced initially and the dose increased slowly to a maximum of 250 mg/day. The high doses of benzodiazepines were gradually withdrawn. She commenced the second series of ECT sessions on the 108th day of her hospital admission. Up until this time she continued to show features of mania and malignant catatonia. She was highly agitated and physically aggressive on several occasions. A minimum of 2 staff members were constantly required to closely observe her and minimally restrain her for long periods to prevent harm to herself or others. She fluctuated from periods of overactivity to muteness and rigidity. Her food

and fluid intake were poor and she was haemodynamically unstable. She was pyrexial, confused, and disoriented most of the time. There were increasing concerns that she would collapse from exhaustion.

She received 11 sessions of ECT with the same machine and the duration of her seizures increased. The ECT dose varied between 100 and 140% and the impedance varied between 1700 and 2700 ohms. The seizures lasted 22 to 40 seconds in all sessions and the total seizure time was 369 seconds. She was administered flumazenil 500 µg during the initial 6 sessions of ECT to reverse the effects of the benzodiazepines. Her mental state improved and a significant response was noted by the 3rd session of ECT. She was less agitated, less disinhibited, slept better, and she began to eat and drink better. By the 11th session of ECT there was almost complete resolution of her symptoms.

The most significant residual symptom for Mrs B was difficulty concentrating and remembering past events. A dense amnesia for events during admission was maintained. She was discharged from hospital and is regularly followed up in the outpatient clinic to assess and monitor her mental state. She has been maintained on clozapine at a dosage of 250 mg/day. Psychometric testing is demonstrating a gradual improvement in her cognitive functioning. Her activity levels are increasing, however, she is still unable to sustain high levels of concentration. As yet she has not been able to resume interests such as reading novels.

Discussion

Catatonia is reported to be associated with several disorders and drugs. Although traditionally linked with schizophrenia, several studies have shown that catatonia is more commonly associated with mood disorders.^{2,11} Several drugs are reported to precipitate catatonia such as antipsychotics (typical and atypical including clozapine), antidepressants (tricyclics, monoamine oxidase inhibitors), anticonvulsants (carbamazepine, primidone), disulfiram, dopamine agonists (metaclopramide), dopamine depleters (e.g. tetrabenazine), lithium carbonate, morphine, hallucinogens (lysergic acid diethylamide, phencyclidine), stimulants (amphetamine, methylphenidate) and steroids.^{1,2,12} Mrs B was on several of the medications mentioned above, any of which could have triggered or accelerated the onset of catatonia.

Mania with catatonic features is an important differential diagnosis to be considered in this case. Her clinical features such as pyrexia, confusion, disorientation, and haemodynamic instability support the diagnosis of mania and malignant catatonia. There are several case reports and case series describing the use of a combination of ECT and clozapine for treatment of mood disorders, schizophrenia, and schizoaffective disorders.¹³⁻¹⁵ We believe that we are the first to report the use of the combination to treat malignant catatonia. The mechanism of action of the combination of ECT and clozapine is unclear. It has been suggested that ECT increases the permeability of the blood-brain barrier, permitting psychotropic medications to cross

more effectively and thus enhancing their effectiveness.¹⁵ It is also possible that clozapine simply reduces the seizure threshold and prolongs the duration of seizures making ECT more effective. Whether the combination may have a more complex effect on the neurotransmitters in the brain is as yet unknown. As the neurochemical or physiological changes in catatonia remain unclear, the mechanisms of action of the effective treatments of catatonia are little understood. As clozapine reduces the seizure threshold of the brain, one must bear in mind the risk of status epilepticus on administration of ECT.¹⁶

There exists a growing body of evidence reporting adverse effects of ECT on cognitive function. Mrs B reports retrograde amnesia and loss of autobiographical memory of events during and immediately before ECT. This fits with our current knowledge of the adverse cognitive effects of ECT. There is general consensus that memory loss is the most commonly reported side-effect of ECT.¹⁷ Prior to treatment with ECT, Mrs B fluctuated in and out of a delirious state with gross deficits in her concentration and memory. Following treatment, repeated psychometric testing has demonstrated a gradual recovery of cognitive functioning over time.

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